1,147,295

PATENT SPECIFICATION

NO DRAWINGS

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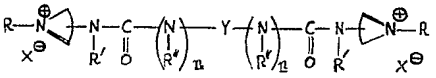
COMPLETE SPECIFICATION

Process for the production of Bis-Quaternary Ammonium Compounds

We, FARBENFABRIKEN BAYER AKTIENGESELLSCHAFT, a body corporate organised under the laws of Germany, of Leverkusen, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed to be particularly described in and by the following statement:—

The present invention relates to novel bis-quaternary ammonium compounds and pharmaceutical compositions containing a cytostatic or trypanocidal amount thereof which are useful in the treatment of a variety of parasitic diseases caused by trypanosomes and of neoplastic diseases, especially of leukemia.

It has now been found that bis-quaternary ammonium compounds of the formula:



in which

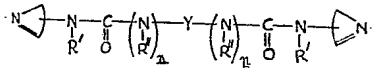
is a pyridine, quinoline, *iso*quinoline, indolenine, benzoxazole, benzothiazole, benzimidazole or acridine ring which is unsubstituted or substituted by at least one halogen atom, or an alkyl, aryl, alkoxy, alkylmercapto, nitro, acylamino, carbonamido, carbalkoxy, sulphonamido, alkylsulphone or trifluoromethyl group or groups; R is an alkyl radical; R′ and R″ which may be the same or different are hydrogen or an alkyl radical; X is the radical of an inorganic or organic acid; Y is a saturated or unsaturated alkylene, arylene, cycloalkylene, aralkylene, hexahydro-aralkylene or heteroarylene group which is unsubstituted or substituted by at least one halogen atom or an alkyl, alkoxy, alkylmercapto, hydroxyalkyl, haloalkyl, nitro, substituted or unsubstituted amino, carbalkoxy, carbonamide, sulphonamide or alkylsulphone group or groups and *n* is 0 or 1, have valuable therapeutic properties in that they exhibit a marked cytostatic and, in addition, a broad trypanocidal activity against a variety of trypanosomes causing parasitic diseases.

The amount or dosage and route of administration of the new compounds will be understood by those skilled in this art and are similar to those used for known trypanocidal agents such as germanin, neoarsphenamine and thioarsenites.

In contradistinction thereto, the known N,N′ - bis - [quinolyl - (6)] - carbamide-bis - methosulphate used for the treatment of bovine piroplasmosis [cf. F. Schönhöfer and H. Henecka in "Medizin und Chemie", Volume IV, Verlag Chemie Berlin (1942), pages 156 to 163] has no appreciable cytostatic or trypanocidal activity.

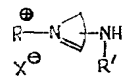
The new cytostatic and trypanocidal compounds of the present invention are prepared in several different ways by reacting:—

(a) a bis-substituted dicarboxylic acid diamide or bis-urea of the formula:

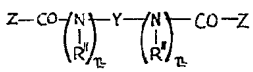


with a reactive ester RX; or

(b) a quaternary amino-heterocycle of the formula:



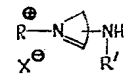
with a reactive derivative of a dicarboxylic acid of the formula:



in which Z is an atom or group reacting with the group N(R')H with the elimination of HZ;

or

(c) when n is 1 and R'' is hydrogen, reacting a quaternary amino-heterocycle of the formula:

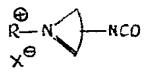


with a bis-isocyanate of the formula

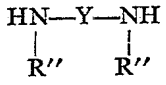
OCN—Y—NCO;

or

(d) when n is 1, and R' is hydrogen, reacting a quaternary isocyanato-heterocycle of the formula:



with a diamine of the formula:



wherein

R, R', R'', X, Y and n have the above stated meanings.

The method (a) is carried out without or in the presence of a suitable solvent or diluent at a temperature between 20 and 200°C. Nitrobenzene has proved to be a particularly suitable reaction medium, and the most advantageous range of temperature is 70 to 150°C. The use of an excess of the compound RX is advantageous, in order to achieve a complete bis-quaternization. Suitable compounds RX are, for example, methyl iodide, ethyl iodide, dimethyl sulphate, diethyl sulphate, methane-sulphonic acid methyl ester, *p*-toluene-sulphonic acid methyl ester, and benzene-sulphonic acid ethyl ester.

The method (b) is also carried out without or in a solvent or diluent, for example, in benzene, dioxan or dimethyl formamide, and when a dicarboxylic acid chloride is used, it is expedient to add an inorganic or tertiary organic base, in order to bind the hydrogen chloride formed. The reaction temperature primarily depends on the nature of the dicarboxylic acid derivative used; in general, a dicarboxylic acid chloride reacts at between 0 and 50°C, whereas a dicarboxylic ester usually requires a higher temperature for the reaction.

The methods (c) and (d) are expediently carried out in solvents or diluents which do not react with isocyanate groups in the range of temperature applied, for example, in benzene, dioxan or tetrahydrofuran. The reaction temperature primarily depends on the nature of the isocyanate used and lies usually between 0 and 100°C. The products of the process so obtained can be separated from the reaction mixture by filtration, since they are sparingly soluble in most organic solvents in the cold. If necessary, purification can subsequently be carried out by recrystallization from water, dimethyl formamide or mixtures of both, or also from water/ethanol or water/acetone. The anions of the bis-quaternary ammonium compounds obtained can be exchanged in known manner by reaction with appropriate acids or alkali metal salts.

The invention also provides a typanosidal and/or cytostatic pharmaceutical composition comprising an effective amount of a compound of the invention in admixture with a carrier or diluent.

The invention further provides a method of treating trypanosomiasis in animals which comprises administering to an infected animal an effective amount of the above composition. The antileukemic effect of the compounds:

FB a 2694=N,N' - bis[quinolyl - (6)] - terephthalic acid diamide - bis-methosulfate (Example 1)

FB a 6469=N,N' - bis [1 - methyl - benzimidazolyl - (5)] - terephthalic acid diamide - bis - methosulfate (Example 4)

FB a 6645=N,N' - bis [quinaldyl - (6)]-teraphthalic acid diamide - bis-methosulfate (Example 3)

has been tested against leukemia L 1210 of mice. Mice of the strain B 6 D 2 Fl with the aspect of lymphatic leukemia have been treated by 4 intraperitoneal injections of the following doses of the above compounds. The antileukemic effect have been determined by calculating the average survival times (AST 50) of the treated groups and the control groups.

If
100% means the AST 50 of the control group
<100% means a shortened AST 50 of the control group and
>100% means a prolonged AST 50.

The results of these tests are given in the following table:

FB a-No.	Dose *p.d.* mg/kg	Frequency Application	Index of effect %	Surviving animals Number/Months
2694	8	4 x, i.p.	131,3	
	15	„	268,8	2/ 9
	30	„	366,7	2/10
	40	„	698	5/12
	80	„	113,3	
6469	30	„	113,3	
	60	„	181,3	
	80	„	133,3	
6645	10	„	153,3	
	20	„	33,3	

By treatment of the Ehrlich carcinoma with similar dosages as above substantial inhibition of the tumor growth have been obtained.

Trypanocidal effect of the compounds

FB a 2694=N,N′ - bis - [quinolyl - (6)]-terepthalic acid diiamide - bis-methosulfate (Example 1) and
FB a 2643=N_2,N_2′ - Phenylene - bis-[quinolyl - (6) -] - urea - bis-methosulate (Example 2)

The compounds have been tested against the experimental infection of mice with *Trypanosoma congolense* and with *Trypanosoma brucei*. Mice with a weight of 18—22 grams have been used.

The mice were treated one day after the infection by a single subcutaneous dose of an aqueous suspension of 0,1 g substance with 0,2 cc. Cremophor. (The word "Cremophor" is a Registered Trade Mark). The infection process was watched by means of daily microscopical blood tests and of the survival times of the treated animals in comparison with those of the untreated control animals. The tests have been evaluated according to the following lines:

+=dead, *dosis letalis*
3=healing, i.e. the trypanosomae disappeared after the treatment for at least 21 days
2=effective, i.e. the trypanosomae disappeared from the blood after the treatment for less than 21 days, or the test animal, which became free of trypanosomae, died within a period of 21 days.
1=less effective, i.e. the trypanosomae are permanently traceable, but in a lesser number than in the untreated controls, or the survival time is prolonged at a fairly constant number of trypanosomae
0=without any effect, i.e. the infections process is the same as in the untreated animals

TABLE

Effect against Trypanosoma congolense

compound	dose mg/kg 1000	500	250	100	50	25	10	5
FB a 2694	3	3	3	2	2	2	0	
FB a 2643			+	3	3	3	3	0

Effect against Trypanosoma brucei

compound	dose mg/kg 1000	500	250	100	50	25	10	5	2,5	1	0,5	0,25
FB a 2694	3	3	3	3	3	3	3	3	2	2	1	0
FB a 2643			+	3	3	3	3	1	2	0		

Acute toxicity:

The maximum tolerated dose in mg/kg on the healthy mouse are:

	per os	subcutan
FB a 2694	1000	1000
FB a 2643	1000	250
FB a 6469	1000	100

The invention is illustrated by the following non-limitative examples.

EXAMPLE 1.

A suspension of 50.8 g (0.25 mole) of terephthalic acid chloride in 250 ml of pyridine is added in portions at about 10°C with stirring to 79.2 g (0.55 mole) of 6-aminoquinoline dissolved in 250 ml of pyridine, stirring is continued at room temperature for 15 hours and at 50°C for 1 hour, the mixture is poured into 1 liter of water, adjusted to pH 9 by the addition of a 10% sodium carbonate solution, and the precipitate is filtered off with suction. After thoroughly washing with water and then with methanol and drying at 100°C, a colorless finely crystalline powder is obtained of m.p. 350°C. The yield of N,N' - bis-[quinolyl - (6)] - terephthalic acid diamide amounts to 95.0 g=90% (105.0 g).

41.8 g (0.1 mole) of the above compound are stirred in 500 ml of nitrobenzene with 50.4 g (0.4 mole) of dimethyl sulphate at 120°C for 4 hours. After cooling, the reaction product is filtered off with suction and thoroughly washed with acetone. A colorless finely crystalline power is obtained of m.p. 350°C. The yield of N,N' - bis - [quinolyl - (6)] - terephthalic acid diamide - bis - methosulphate amounts to 61.8 g=92% (67.1 g).

EXAMPLE 2.

A suspension of 8.0 g (0.05 mole) of phenylene - (1,4) - diisocyanate in 50 ml of benzene is added in portions to a solution of 14.4 g (0.1 mole) of 6-aminoquinoline in 50 ml of benzene, and the mixture is heated under reflux for one hour while stirring. After cooling, the precipitate is filtered off with suction and washed with benzene. A colorless finely crystalline powder is obtained of m.p. 350°C. The yield of N_2, N_2' - phenylene - 1,4 - bis-[quinolyl - (6) - urea] amounts to 20.5 g= 91% (22.4 g).

20.4 g (0.0455 mole) of the above compound are stirred in 180 ml of nitrobenzene with 17.2 g (0.137 mole) of dimethyl sulphate for 4 hours at an external temperature of

120°C, the precipitate is filtered off with suction after cooling, and thoroughly washed with acetone. A slightly yellow-colored powder is obtained of m.p. 230°C (decomposition). The yield of N_2, N_2' - phenylene - 1,4 - bis-[quinolyl - (6) - urea] - bis - methosulphate amounts to 29.0 g=91% (31.7 g).

EXAMPLE 3.

15.8 g (0.1 mole) of 6-aminoquinaldine are dissolved in 100 ml of pyridine and there are introduced in portions at a temperature of 10/15°C 10.2 gs (0.05 mole) of terephthalic acid dichloride. This is stirred for 18 hours at room temperature and then for 1 hour at 50°C, the mixture poured into water and made alkaline with soda solution. The precipitate is suction filtered, washed with water and recrystallized from dimethyl formamide. There are obtained 9.7 g (43% of theory) N,N' - bis-[quinaldyl - (6)] - terephthalic acid diamide as a colorless powder of m.p. 345/350°C (decomposition).

9.4 g (0.021 mole) of the foregoing compound in 100 ml of nitrobenzene are heated with 8.4 ml of dimethyl sulphate under stirring for 4 hours at 140°C and after cooling the precipitate is suction filtered and washed with acetone. There are obtained 13.6 g (93% of theory) of N,N' - bis[quinaldyl - (6)] - terephthalic acid diamide - bis - methosulphate as a light beige powder of m.p. 195°C (decomposition).

EXAMPLE 4.

From 1 - methyl - 5 - amino - benzimidazole and terephthalic acid dichloride there is obtained, similarly to Example 1, N,N'-bis[1 - methyl - benzimidazolyl - (5)] - terephthalic acid diamide as a colorless powder of m.p. >360°C in a yield of 95% of theory. Similarly to Example 1, this is converted with dimethyl sulphate in nitrobenzene to N,N'-bis[1 - methyl - benzimidazolyl - (5)] - terephthalic acid diamide - bis - methosulphate of m.p. >360°C (decomposition).

EXAMPLE 5.

8.4 g (0.02 mole) of N,N' - bis[quinolyl-(6)] - terephthalic acid diamide in 100 ml of nitrobenzene are stirred with 10.4 ml of diethyl sulphate for 4 hours at 120°C and after cooling the precipitate is suction filtered and washed with acetone. There are obtained 9.9 g (68% of theory) of N,N' - bis[quinolyl-(6)] - terephthalic acid diamide - bis - ethosulphate of m.p. >360°C.

EXAMPLE 6.

Similarly to Example 5, there is obtained from N,N' - bis[quinolyl - (6)] - terephthalic acid diamide and methanesulphonic acid methylester in nitrobenzene the compound N,N' - bis - [1 - methylquinolinium - (6)]-terephthalic acid diamide - bis - methanesulphonate as a colorless fine crystalline powder of m.p. 348°C (decomposition). By dissolving this substance in water and adding an excess of hydrochloric acid, there precipitates N,N' - bis-[quinolyl - (6)] - terephthalic acid diamide-bis-methochloride as a colorless powder of m.p. 315°C (decomposition).

EXAMPLE 7.

Similarly to Example 3, there is obtained from 6-amino-quinoline and 2-nitroterephthalic acid dichloride the compound N,N' - bis-[quinolyl - (6)] - 2 - nitroterephthalic acid diamide as a light yellow powder of m.p. 292°C (decomposition) and therefrom by reaction with dimethyl sulphate the compound N,N' - bis[quinolyl - (6)] - 2 - nitroterephthalic acid diamide-bis-methosulphate as a colorless powder of m.p. 278°C (decomposition).

EXAMPLE 8.

Similarly to Example 3, there is obtained from 6-aminoquinoline and 2-chloroterephthalic acid dichloride the compound N,N'-bis[quinolyl - (6)] - 2 - chloroterephthalic acid diamide as a colorless powder of m.p. 274°C (decomposition) and therefrom by reaction with dimethyl sulphate the compound N,N'-bis[quinolyl - (6)] - 2 - chloroterephthalic acid diamide - bis - methosulphate as a colorless powder of m.p. 280°C (decomposition).

EXAMPLE 9.

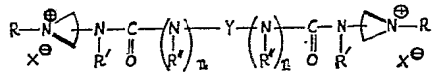
Similarly to Example 3, there is obtained from 2 - methyl - 6 - aminobenzthiazol and terephthalic acid dichloride the compound N,N' - bis[2 - methyl - benzothiazolyl - (6)]-terephthalic acid diamide of m.p. 285°C (decomposition) and therefrom by reaction with dimethyl sulphate the compound N,N' - bis-[2 - methylbenzothiazolyl - (6)] - terephthalic acid diamide-bis-methosulphate as a colorless powder of m.p. >350°C.

EXAMPLE 10.

Similarly to Example 3 there is obtained from 6-aminoquinoline and furan-2,5-dicarbonic acid dichloride as a colorless powder the compound N,N' - bis[quinolyl - (6)]-furandicarbonic acid diamide as a colorless powder of m.p. >260°C (decomposition) and therefrom by reaction with dimethyl sulphate in nitrobenzene the compound N,N' - bis-[quinolyl - (6) - furandicarbonic acid diamide-bis-methosulphate as a colorless powder of m.p. 353°C (decomposition).

WHAT WE CLAIM IS:—

1. Compounds of the general formula:—



in which

is a pyridine, quinoline, *iso*quinoline, indolenine, benzoxazole, benzothiazole, benzimidazole or acridine ring; unsubstituted or substituted by at least one halogen atom or an alkyl, aryl, alkoxy, alkylmercapto, nitro, acylamino, carbonamido, carbalkoxy, sulphonamido, alkylsulphone, or trifluoromethyl group or groups;

R is alkyl;

R′ and R″, which may be the same or different, are hydrogen or alkyl;

X is the radical of an inorganic or organic acid;

Y is a saturated or unsaturated alkylene, arylene, cycloalkylene, aralkylene, hexahydroaralkylene or heteroarylene group, unsubstituted or substituted by at least one halogen atom or an alkyl, alkoxy, alkylmercapto, hydroxyalkyl, haloalkyl, nitro, or substituted or unsubstituted amine, carbalkoxy, carbonamide, sulphonamide, or alkylsulphone group or groups; and

n is 0 or 1.

2. N,N -bis[quinolyl - (6)] - terephthalic acid diamide bis-methosulphate.

3. N_2,N_2′ - phenylene - 1,4 - bis[quinolyl-(6) - urea] - bis - methosulphate.

4. N,N′ - bis[quinaldyl - (6)] - terephthalic acid diamide-bismethosulphate.

5. N,N′ - bis[1 - methyl - benzimidazolyl-(5)] - terephthalic acid diamide-bis-methosulphate.

6. N,N′ - bis[quinolyl - (6)] - terephthalic acid diamide-bis-ethosulphate.

7. N,N′ - bis[quinolyl - (6)] - terephthalic acid diamide-bis-methochloride.

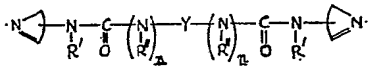
8. N,N′ - bis[quinolyl - (6)] - 2 - nitro-terephthalic acid diamide-bis-methosulphate.

9. N,N′ - bis[quinolyl - (6)] - 2 - chloro-terephthalic acid diamide-bis-methosulphate.

10. N,N′ - bis[2 - methylbenzothiazolyl-(6)] - terephthalic acid diamide-bis-methosulphate.

11. N,N′ - bis[quinolyl - (6)] - furandicarbonic acid diamide-bis-methosulphate.

12. A process for the preparation of the compounds of any of claims 1 to 11, wherein a bis-substituted dicarboxylic acid diamide or bis-urea of the formula:



is reacted with a reactive ester RX, in which formulae the symbols

R, R′, R″, X, Y and *n* each have the meanings given in claim 1, at a temperature between 20°C and 200°C.

13. The process of claim 12 whenever carried out in nitrobenzene as solvent or diluent.

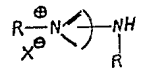
14. The process of claim 12 or 13 whenever carried out at between 70°C and 150°C.

15. The process of claim 12, 13 or 14 wherein an excess of the ester RX is present at the beginning of the reaction.

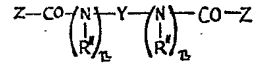
16. The process of any of claims 12 to 15 substantially as hereinbefore described in any of Examples 1, 2, and 3.

17. The process of any of claims 12 to 15 substantially as hereinbefore described in any of Examples 4 to 10.

18. A process for the preparation of the compounds of any of claims 1 to 11, wherein a quaternary amino-heterocycle of the general formula:



is reacted with a reactive derivative of a dicarboxylic acid of the general formula:



in which formulae the symbols

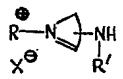
R, R′, R″, X ,Y, and *n* each have the meanings given in claim 1, and Z is an atom or group reacting with the group N(R′)H to eliminate HZ.

19. The process of claim 18, wherein a dicarboxylic acid chloride is used in the presence of an inorganic or tertiary organic base to bind evolved hydrogen chloride.

20. The process of claim 19 whenever carried out at from 0 to 50°C.

21. A process for the preparation of the compounds of claims 1 to 11, wherein *n* is

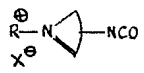
1 and R'' is hydrogen, in which a quaternary amino-heterocycle of the formula:



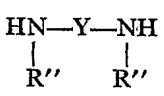
is reacted with a bis-isocyanate of the formula OCN—Y—NCO, in which general formula

R, R', X and Y have the meanings given in claim 1.

22. A process for the preparation of the compounds of claims 1 to 11 wherein n is 1 and R' is hydrogen, in which a quaternary isocyanate-heterocycle of the formula:



is reacted with a diamine of the formula:



in which general formula

R, R'', X and Y have the meanings given in claim 1.

23. The process of claim 21 or 22 whenever carried out at 0 to 100°C in a solvent or diluent which does not react with the isocyanate at the reaction temperature.

24. The compounds of any of claims 1 to 3 whenever prepared by the process of any one of claims 12 to 16 and 18 to 23.

25. The compounds of any one of claims 4 to 11 whenever prepared by the process of claim 17.

26. A trypanocidal and/or cytostatic pharmaceutical composition comprising as an active ingredient an effective amount of a compound of any of claims 1 to 3 and 24 or 25 in admixture with a carrier or diluent.

27. A method of treating trypanomiasis in animals which comprises administering to an infected animal an effective amount of the composition of claim 26.

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